PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Applicant's or agent's file reference see form PCT/ISA/220	Date of mailing *(day/month/year)* see form PCT/ISA/210 (second sheet) **FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP2005/051340	23.03.2005	25.03.2004

International Patent Classification (IPC) or both national classification and IPC
A61K9/20, A61K31/64

Applicant
FERRER INTERNACIONAL, S.A.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

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Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

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Box No. V Reasoned statement under Rule 43*bis*.1(a)(I) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	-
	No:	Claims	1-7, 11-15
Inventive step (IS)	Yes:	Claims	-
	No:	Claims	8-10
Industrial applicability (IA)	Yes:	Claims	1-15
	No:	Claims	-

2. Citations and explanations

see separate sheet

V Reasoned statement under Rule 66.2 (a) (ii) with regard to novelty, inventive step or industrial applicability

1) Documents
The following documents (D1-D3) are referred to in this communication; the numbering will be adhered to in the rest of the procedure:

D1: US 2003/153608 A1 (MAEGERLEIN MARKUS ET AL) 14 August 2003 (2003-08-14)
D2: US 2003/118648 A1 (HIRSH JANE ET AL) 26 June 2003 (2003-06-26)
D3: WO 03/035029 A (DEPOMED, INC) 1 May 2003 (2003-05-01)

Unless otherwise specified, reference is made to the respective cited passages in D1-D3 (see the International Search Report, Form PCT/ISA/210).

2) Novelty - Article 33 (1) and (2) PCT

2.1) D1 discloses a stable solid or semisolid pharmaceutical preparation which may be suitable for the modified-release of the active agent and which comprises 0.5-95 wt % or 5-25 wt % torasemide in an essentially noncrystalline form and polymers as Eudragit RL have been used for matrix delayed-release tablets in example 8. The composition additionally contains binders and magnesium stearate as lubricant.

D2 refers to sustained release formulations comprising an active agent, such as torasemide and a polymer, such as cellulose, acrylate or methacrylate derivatives. A binder solution (e.g. based on polyvinyl pyrrolidone) and a lubricant are used for the granulation process.

With D3 an erodible, gastric-retentive dosage form is shown which comprises a biocompatible, hydrophilic polymer being based on polyacrylamide, poly (alkyl methacrylates), poly (alkyl cyanoacrylates) and having the active agent (such as torasemide) incorporated therein. The addition of diluents, binders, disintegrants, lubricants (magnesium stearate, talc) is described.

2.2) In the light of D1 -D3 (see sections V-1, 2.1), the subject-matter of claims 1-7, 11-15 is considered not novel a

according to Article 33(1) and (2) PCT

2.3) Consequently, the subject-matter of claims 8-10 appears to be novel (Article 33 (1), (2) PCT), since its corresponding content is not disclosed by D1-D3.

3) Inventive Step - Article 33 (1) and (3) PCT

3.1) The problem posed in the present application was the avoidance of troublesome urinary urgencies caused by immediate-release torasemide preparations.

The solution according to the Applicant was a prolonged-release formulation comprising torasemide

and a matrix-forming polymer.

a) D1 which is regarded closest prior art discloses a stable solid or semisolid pharmaceutical preparation which may be suitable for the modified-release of the active agent and which comprises 0.5-95 wt % or 5-25 wt % torasemide in an essentially noncrystalline form and polymers as Eudragit RL has been used for matrix delayed-release tablets in example 8. The composition additionally contains magnesium stearate as lubricant and binders.

D1 does not disclose the percentages of the polymers and the use of guar gum as matrix polymer.

It appears to be obvious to a person skilled in the art to derive the polymer concentrations and the inclusion of guar gum in said compositions.
Unexpected or surprising effects do not seem to be connected with said concentrations and polymers.

b) Alternatively, D3 can be regarded as closest prior art describing an erodible, gastric-retentive dosage form which comprises a biocompatible, hydrophilic polymer being based on polyacrylamide, poly (alkyl methacrylates), poly (alkyl cyanoacrylates) and having the active agent (such as torasemide) incorporated therein. The addition of diluents, binders, disintegrants, lubricants (magnesium stearate, talc) is described.
D3 does not foresee concrete torasemide and polymer concentrations for the formulation intended.
Since no unexpected or surprising effects seem to be connected with, the person skilled in the art derive those from the pharmacokinetic data, from the experience in galenical science and the requirements of the formulation.

3.2) Therefore, the subject-matter of claims 8-10 is obvious to a person skilled in the art due to general textbook knowledge

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Thus the amendment submitted - matter does no

t m e e t t h e r e q u i r e m e n t s o f A r t i c l e 3 3 (1) a n d (3) P C

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T i n t h a t e x t e n t t h a t i t c a n n o t b e c o n s i d e r e d i n v e n

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4) Further remarks
The Applicant's attention is drawn to the fact that the application must not be altered thus that its subject-matter might exceed the contents of the application originally filed (Article 41 (2) PCT).